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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/031,801	03/15/93	KUCHERLAPATI R	A-CELL-4.4-U

HM31/1014

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EXAMINER	
HAUDA,K	42

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/031,801	Applicant(s) Kucherlapati et al.
	Examiner Karen M. Hauda	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Jul 2, 1998*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *68, 83-97, and 101-103* is/are pending in the application.

Of the above, claim(s) *68* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *83-97 and 101-103* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *36*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

The request filed on July 2, 1998 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/031,801 is acceptable and a CPA has been established. An action on the CPA follows.

Applicant's response fails to address the rejections of record contained in the office action mailed January 6, 1998, paper #37. Therefore, for the reasons of record all rejections are maintained as set out in the office action mailed January 6, 1998, paper # 37 and re-iterated below for the convienence of applicants.

The suspension of this application is withdrawn in view of the resolution of the potential interference issues and this application is returned to active status. The notice of allowability is being revoked in view of the issued claims directed to similar or overlapping subject matter to Krimpenfort et al., senior party. This current claims in this application are not allowable.

Claims 83-97 and 101-103 are active, and examined in this Office Action. Claims 1-67, 69-82 and 98-100 have been cancelled; claim 68 remains active and non-elected.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 83-97 and 101-103 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for HPRT, does not reasonably provide enablement for a xenogeneic DNA wherein the DNA is a human immunoglobulin gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or practice the invention commensurate in scope with these claims. The specification discloses two hypothetical methods of making xenogeneic heavy chain and xenogeneic light chains, the first method comprising cloning of the human immunoglobulin DNA segments into YACs and the second by construction of a DNA construct containing the human Ig locus. Regarding the first, the specification fails to disclose actual working examples of transgenes cloned into YACs wherein the transgene spans the entire human Ig locus and is capable of undergoing isotype switching. This ground of rejection is necessitated by the issuance of the patents to Lonberg containing the Cox declaration which states that the human immunoglobulin DNA locus as described in the instant specification was not, and could not, be cloned at the time the claimed invention was made, and secondly, in view of references with significantly later postfiling publication dates specifically stating that isotype switching to downstream isotypes had not yet been achieved using the described human Ig loci contained in YACs.

The Cox declaration states that there were no reports of the cloning in YAC vectors of the region spanning the human delta and gamma3 genes. This region is not readily or predictably cloned and the problem, as explained by the declarant, is possibly due to instability of that region of the human genome in certain cloning vectors, such as YACs. Thus, the art had not reported the cloning of an intact human IgH locus containing the V, D, J, mu, delta and gamma sequences, let alone an intact human IgH locus cloned in a YAC.

The published art was not aware of how to make a transgenic animal containing a transgene construct containing human Ig genes capable of undergoing isotype switching to produce human isotypes downstream of IgM as evidenced by Taki et al (1993), disclosing that the authors did not know how to make a transgene that could undergo cis-isotype switching where

endogenous sequences were not involved. Morrison, writing a review of the field in Nature (1994), discussed the teachings of Green et al., which referenced two Kucherlapati published PCT applications, (page 812, column 2, bottom):

"In Green and colleague's mice, only the mu heavy chain contributes significantly to the circulating antibody population, and these mice are unable to undergo the isotype switching characteristic of the mature antibody response. But in the mice of Lonberg et al., the heavy-chain locus contains both a mu and gamma1 heavy chain with switch sites, and these authors show that class switching occurs. So they have reconstituted the essential part of a human-antibody-producing response in a mouse and the system could be used both to study control of antibody production as well as to produce specific human antibodies".

In view of the foregoing, the instant specification was not enabling for the human IgH locus containing the V, D, J, mu, delta and gamma sequences cloned into a YAC nor for a transgenic animal containing the IgH locus-YAC. The specification fails to disclose which of the sequences are necessary to obtain a DNA capable of producing a functional antibody. Although all the claimed regions, i.e., J, D, constant are known in the art, the specification fails to disclose how to operably link the sequences together to obtain a DNA encoding a functional antibody. The specification hypothetically discloses the cloning of an intact human IgH locus containing the V, D, J, mu, delta and gamma sequences into a YAC vector, which as discussed above, was not enabled at the time the claimed invention was made.

The specification of the instant application regarding the actual production of transgenic mice containing human immunoglobulin genes produced by fusion of spheroplasts containing YACs with ES cells is speculative and does not present any working examples showing actual cloning of human immunoglobulins and that if such mice were actually obtained, that human antibodies would be expressed from the human IgH locus. In view of the lack of actual working examples and evidence presented showing that the DNA containing the human immunoglobulin locus could not be obtained by applicant's method at the time the claimed invention was made, the specification is not enabling for the method, or animals produced by the method, as claimed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 83, 85, 89 and 91 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S.P.N. 5,591,669 to Krimpenfort et al. Krimpenfort discloses gene targeting of the J region of endogenous heavy chain immunoglobulin alleles in ES cells and further discloses that the embryonic stem (ES) cells having the inactivated J region endogenous alleles produce mice incapable of producing endogenous (murine) immunoglobulins.

Regarding claims 89 and 91, Krimpenfort discloses use of mice.

Regarding claims 83 and 85, "lesions in the J region" are disclosed in Krimpenfort in column 8, lines 10-16 as deletions in part of the D and/or J segments of the variable region; in column 9, lines 35-45, wherein preferably all of the variable region is deleted although small segments of 5' sequences encoding an N-terminal portion of the V segment and 3'sequences encoding the C-terminal portion of the J segment may be retained in the transgene used to effect the inactivation; in column 10, lines 5-13, as mutations involving the insertion or deletion of one or more nucleotides which result in frame shift mutation, or insertion of a stop codon, and, in claim 5 wherein deletions of the J region are specifically claimed.

Regarding the ability of the locus to rearrange, insertion of a neo gene into the J region, insertion of a stop codon into the J region, and deletion of a nucleotide or nucleotides in the J region are all functional equivalents with respect to inhibition of rearrangement since in each of the 3 instances the J region is no longer a functional domain. Krimpenfort discloses that lack of any functional domain in the variable region would result in inactivation of endogenous immunoglobulin expression (column 4, lines 36-39).

Therefore, the reference anticipates the claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 84, 86-88, 90, 92-97 and 101-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krimpenfort as applied to claims 83, 85, 89 and 91 above, and further in view of Krimpenfort (U.S.P.N. 5,591,669). Claims 83, 85, 89 and 91 were rejected under 35 U.S.C. 102(e) for reasons as stated above. Krimpenfort discloses that the immunoglobulin light chain variable region contains V and J segments in column 2, lines 13-15, and further discloses in column 10, lines 66-67, that the genes encoding the various segments and regions which may be used in the invention are well characterized. Krimpenfort discloses inactivation of the J region of the endogenous immunoglobulin heavy chain in ES cells and mice produced from those ES cells. Krimpenfort differs from the claim in that the reference fails to disclose inactivation of the J region of the immunoglobulin light chain. However, it would have been obvious to one of ordinary skill to inactivate the light chain J region using the techniques taught by Krimpenfort since Krimpenfort discloses that the genes encoding the various segments and regions which may be used in the

invention are well characterized and further that lack of functional domains inhibit rearrangement and thus expression. Krimpenfort provides the motivation for modification of the light chain J region since Krimpenfort discloses that inactivation of the heavy chain J region is "preferable" thereby suggesting that light chain J region inactivation is an enabled and obvious alternative. One of ordinary skill would have had a reasonable expectation of success in obtaining light chain J region inactivation using the techniques of Krimpenfort since Krimpenfort discloses that the genes encoding the various segments and regions are well characterized. Applicant's arguments on the record stating the obviousness of JL knockout over JH knockout are repeated, below.

Regarding claims 86-88, 92-97 and 101-103,, Krimpenfort discloses in column 13, lines 45-end, that transgenes from species (therefore xenogeneic DNA) other than the transgenic animal may be used in the practice of the invention and suggests that the DNA used be from humans. Krimpenfort further discloses use of lymphatic polypeptides encoding both heavy chain and light chains. Krimpenfort discloses cross-breeding to obtain the desired homozygous phenotype.

Accordingly, the modification of the non-human animal of Krimpenfort by inactivation of the J region of the immunoglobulin light chain and insertion of xenogeneic DNA was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention, and therefore, the invention as a whole is prima facie obvious.

Applicant's counsel has established on the record that knockout of the light chain is obvious over knock out of the heavy chain. Applicant's arguments of record are in the amendment filed February 7, 1992. Applicants have argued on the record that light chain J region inactivation is enabled and obvious over heavy chain J region inactivation. In the February 7, 1992 amendment, page 2, third full paragraph, applicants state "There is no reason to believe that

applicants having shown that modification of the locus for the heavy chain at the J region results in inability to rearrange, why this information cannot be extrapolated to one or both of the light chain loci." And further, on page 5, second full paragraph, "However, the examiner has suggested that there is inadequate support for the light chains, as well as claims for other mammals. Other than the fact that they (sic) are light chains, rather than heavy chains, the differences between the loci are not that significant. The loci may be on different chromosomes, but their arrangement is very similar. Therefore, there is a clear expectation that the light loci should respond in the same manner as the heavy loci. Thus applicants should be allowed claims to both light and heavy loci."

Claims 84, 86-88, 90, 92-97 and 101-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krimpenfort as applied to claims 83, 85, 89 and 91 above and further in view of Bruggemann and Lonberg (USPN 5, 545,806). Claims 83, 85, 89 and 91 were rejected for reasons as set forth above. The teachings of Krimpenfort, above, are incorporated herein. The instant set of claims do not specify whether the xenogeneic DNA is unrearranged or rearranged and this rejection addresses the unrearranged xenogeneic DNA. Krimpenfort differs from the claims in that the reference fails to disclose ES cells further comprising a xenogeneic unrearranged human immunoglobulin heavy chain locus capable of producing a functional human immunoglobulin heavy chain wherein the heavy chain is IgM, IgG, IgA, IgE or IgD, or a xenogeneic unrearranged light chain. However, the secondary references, Bruggemann and Lonberg, cure the deficiency. Bruggemann was published on September 1989. Lonberg was filed on August 29, 1990. Applicants are denied their priority dates of parent applications 07/466,008, 07/610,515 and 07/919,297 since the transgene encoding the human IgM and IgG and the expression of human immunoglobulins therefrom was not enabled by applicants. See 112(1) rejection set forth above. Lonberg is therefore proper prior art. Bruggemann discloses an unrearranged transgene encoding human IgM capable of rearranging to produce functional IgM. Lonberg discloses unrearranged transgenes encoding human IgM and transgenes encoding both human IgM and IgG and capable of undergoing isotype switching to produce IgG.

Both Bruggemann and Krimpenfort provide the motivation to combine the references. It would have been obvious to one of ordinary skill to further modify the ES cell of Krimpenfort to additionally express human immunoglobulins of any isotype in view of the teachings of Bruggemann disclosing the desirability of producing human immunoglobulins in mice incapable of producing endogenous murine immunoglobulins (page 6712, column 1, last paragraph). Further, it would have been obvious to one of ordinary skill to modify the ES cells of Krimpenfort to express IgM in view of the teachings of Krimpenfort (column 7, lines 19-27) that transgenes may be used which are capable of facilitating the maturation of the particular lymphocytic cell type which would normally express the cognate endogenous alleles if the lymphatic polypeptide is expressed. It is known in the art that IgM is needed to facilitate lymphocytic cell maturation. Therefore, Krimpenfort teaches the obviousness of adding transgenes encoding IgM to ES cells having inactivated endogenous immunoglobulin gene loci.

Lonberg and Bruggemann provide the reasonable expectation of success in obtaining immunoglobulin expression from the transgenes since Bruggemann discloses that unrearranged human transgene may rearrange to produce functional IgM in a mouse system and since Lonberg discloses that unrearranged human transgenes may rearrange to produce functional IgM and IgG in a mouse system.

Regarding claims 86, 87, 88, 92-97 and 101-103, Krimpenfort discloses knockout of the light chain genes as set forth above. The addition of a human transgene encoding human immunoglobulins is rendered obvious by both of Bruggemann and Krimpenfort for reasons set forth above.

Accordingly, the modification of the ES cell of Krimpenfort by addition of transgenes encoding human immunoglobulins as suggested by Bruggemann and Lonberg to produce a mouse expressing human immunoglobulins and incapable of producing endogenous murine immunoglobulins was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have

had a reasonable expectation of success in producing the claimed invention, and therefore, the invention as a whole is prima facie obvious.

No claim is allowed.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

This application contains claim 68 drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen M. Hauda whose telephone number is (703) 305-6608.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine C. Chambers, may be reached at (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Karen M. Hauda
Patent Examiner
October 5, 1998

BRIAN R. STANTON
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